



Maternal Nutrition & Placental Function

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GATA Kadın Doğum Anabilim Dalı (E)
Ankara



Human Placenta

Discoid Deciduate Haemochorial Chorioallantoic

1. Exchange »

gas

nutrients & waste products

2. Hormonal »

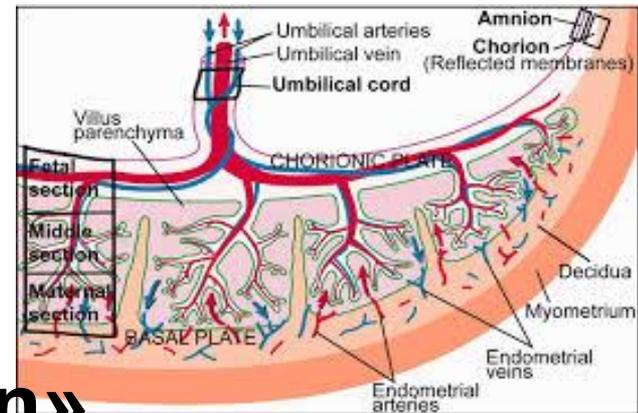
3. Regulation & Modulation»

nutrients

thermoregulation

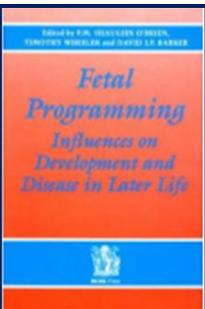
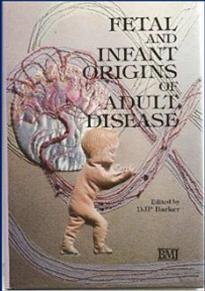
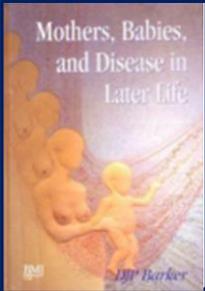
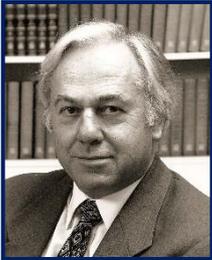
genes

4. Immune » Intrauterine Programming





Developmental Origins of Health and Disease (DOHaD)



- Recent and rapidly changing environmental and disease challenges
- Genetic Factors
- This revisited the peri-conceptual and predisposing
- Sexual Dimorphism



non-communicable
 rs to such
 nt during pre
 ape individual
 dominant for

- McAllister, 2009
- Barker 1990
- Gabory 2009, waddel 2012, Bale 2011, van Abeleen 2011



Nutrients

- **Macro**
 - Carbohydrates, Protein, Lipids
- **Micro**
 - Iron, iodine, selenium, zinc, folate, other vits & factors

Terminology

- **Under** Nutrition (MUN)

» starvation

- **Over** Nutrition (MON)

Mal Nutrition (MMN)



Placenta Fetal developement

Abnormal Nutrient availability

1. High intake

2. Low intake

- Famine, lifestyle, nausea-vomiting

3. Short interpregnancy interval

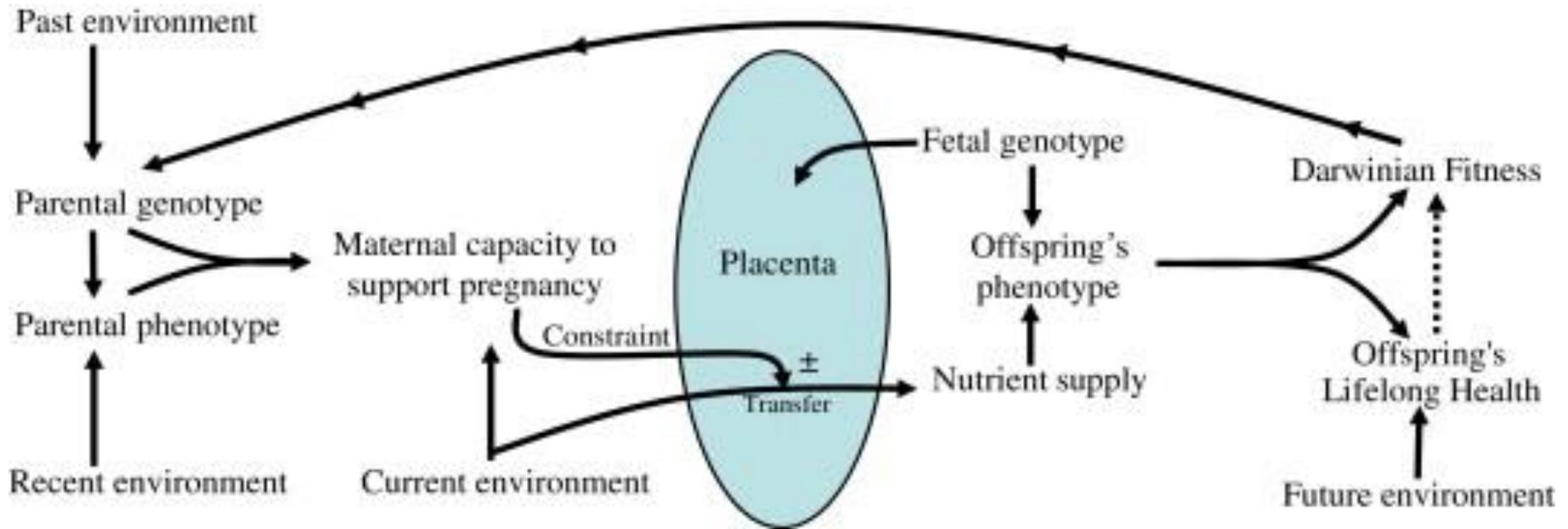
- Nutritional depletion

4. Teenage pregnancy

- Compete food with own fetus
 - ↓ birthweight X2
 - ↑ preterm delivery X3
 - ↑ neonatal mortality X3
 - King 2003



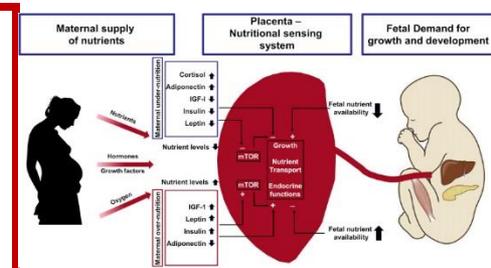
Placental Functions Complex Variables



Levis 2012



Human placenta Syntitium Nutritional Sensing System

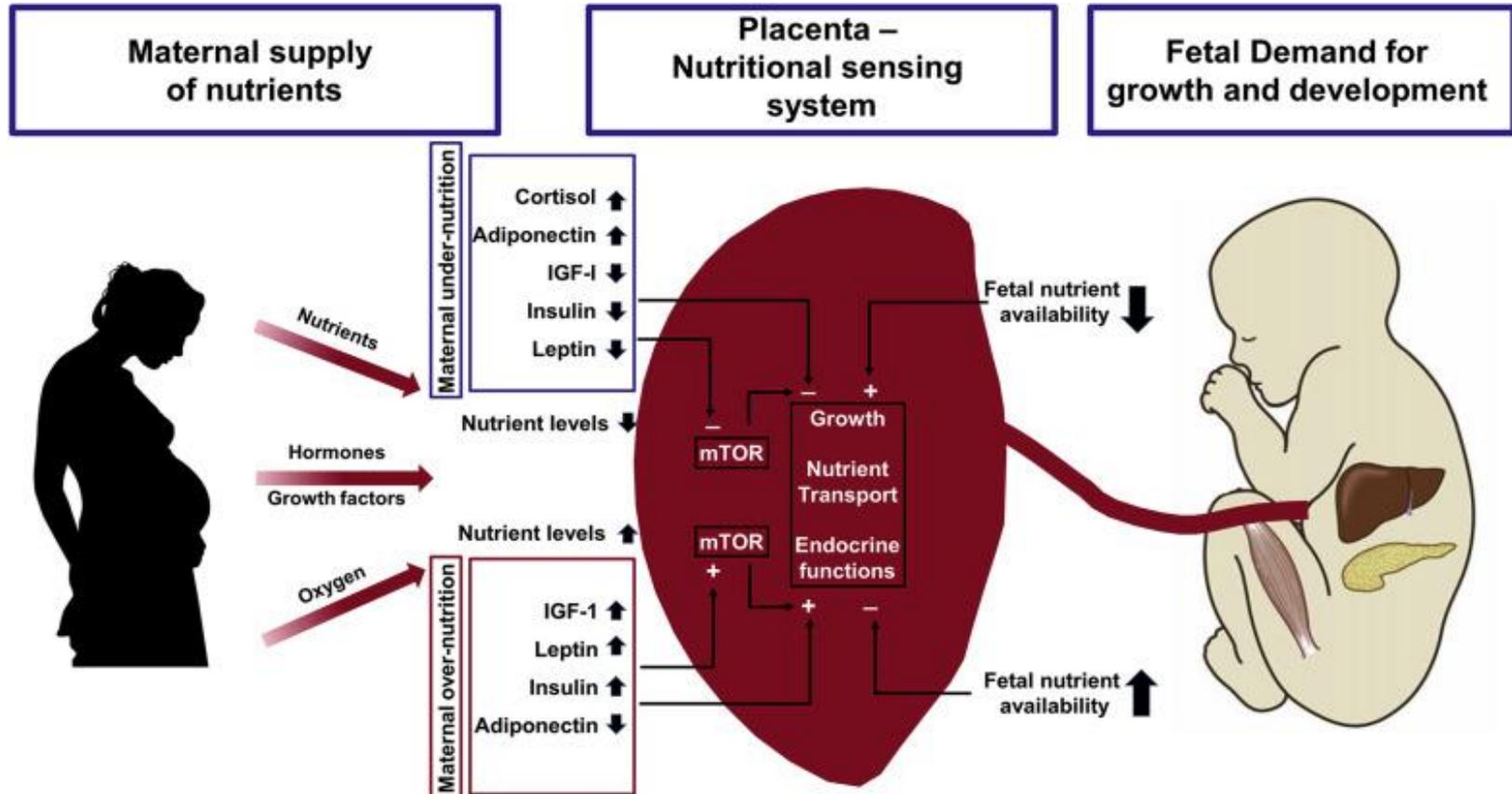


1. Adenosine monophosphate – proteinkinase
 - Global energy
2. Glucogen Synthase3
 - glucose sensor
3. Hexoe Amino signal Pathway
 - glucose, glutamine, acetyl-CoA
4. AA response signal transduction Pathway
 - Ess.AA
5. mTOR (mechanistic Target of Rapamycin) Complex
 - **integrates nutrient and growth factor signaling**



Placental Transfer

Romero R et al 2017





Optimal maternal nutritive supply during pregnancy

Critical role for placental & fetal unit

- Pre Peri Conceptional
 - During pregnancy
 - Early
 - Late
- Various consequences According to Fetal Sex



in Utero Fetal Programming

- Epigenetic
 - Genomic imprinting
- Sexual Dimorphism



Epigenetic

- Impact Life has on the function of Genes
- **1940 Conrad Waddington**
- Interactions between Environment and Genes
 - Gene activity changes
 - Structure of DNA stable
 - Chemical Mechanisms
 - Methylation
 - Histone Post translation Modifications
- **1962 Joel Wallach**
 - Many disease thought genetic transmission infact nutritional deficiency
 - Ricets, scurvy, beriberi [Iacagnia 2018](#)



Epigenetic Mechanism

- **Key molecular mechanism** underlying developmental programming of Fetal Phenotype
- **Heritable gene expression changes** without change in DNA structure
- DNA Methylation (CpG)
 - Covalent modif chromatin
 - Non codingRNA
- Histone Proteins Acetylation
- **Memory of Cell Identity**



Epigenetic Mechanism

- Nutrition, micronutrients, Energy metabolism, external Toxins, Stress,
- **Gametogenesis**
- **Placenta & Conceptus development**
- **Cell identity Changes**
- Delage2008, Choi2010, Gabory 2011, vanHees 2014



Genomic imprinting

- Epigenetic mechanism
- **Parent of Origin Gene Expression**
- **Nutrition linked Transgenerational Effect** on Development and Growth



Sexual Dimorphism

Tarrade 2015

- **MMN**, mat stress etc.. Environmental Factors Affect Males and Females in a Different way
- Bale2011, Aiken2013
- Dimorphism may appear very early during development (Blastocyst) Bennenjo 2010
- Rate of cell division Faster in XY . Mittowitch 1993
- **Maternal Starvation / PI Size & Area** ↓
- More severe for xy Rosenboom 2011
- **Adult Hypertension** Abeleen 2011
- **Metabolic syndrome** More **prevalant** for **xy**
Owens2007



Sexual Dimorphism

Rat Model Zambrano 2013

- High Fructose intake... **Obesity**
- **PI W ↓ Only in males**
- Oleic acid
- ↓ in XY , ↑ in XX
- Some Genes Set For Gender of The Fetus
- X (10 / 34), Y (3 / 7), Autosomes (immun regulation)
 - **Female Placenta more adaptive deleterious environment than Males** Cox 2013



Maternal Mal nutrition (MMN) Placenta (PI)

1. Weight

- **Fetal consequences**

2. Histomorphology

1. Development & Growth

3. Vasculogenesis &

2. Hormone modulation & secretion Angiogenesis

3. Epigenetic Influences

4. Nutrient transfer Capacity 4. Long term Programming on

Progeny



Maternal Undernutrition and Placenta

The Famine Ended 70 Years Ago, but Dutch Genes Still Bear Scars

Belgian born scientist the Dutch Hunger: 'Widow' leaves or adults with higher rates of health problems. New research may have found the genetic switches that made it happen.



A victim of starvation during the Dutch famine of 1944-45. Photos capture today the impact of the famine on those who were affected by health problems throughout their lives.



Hunger kills more people each year than AIDS, malaria and tuberculosis combined. About **21,000 people die of hunger** or related causes **every day.**





Placental Weight (W) Hunger Winter 1944-1945 6 months **Famine** Lumey1998

- Global MUN (avg 400 cal/d), Starvation
- 3rd trimester
 - **PI W ↓ Birth W ↓ PI W/ BW Ratio** **Unaltered**
- Only 1st Trimester
 - **PI W ↑ Birth W Normal PI W/ BW Ratio ↑ Altered**
- **Placental Adaptation in Early Pregnancy**
- Sheep model Similar Observations

Heasman, 1998



Selective Protein Deprivation A Key Factor

Rat Model Langley-Evans, 1996

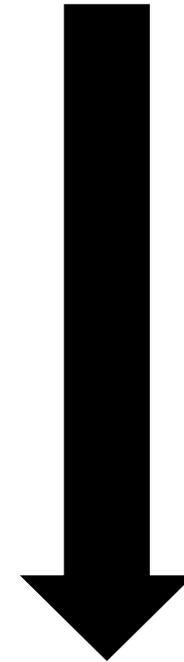
9 – 18 % ↓

- During Pregnancy
- **PI W** ↑ **Fetal Growth** ↓
- Early Pregnancy
- **PI W** ↑ **Fetal Growth** → ↑



Placental Histomorphology Human Observations and Animal Models

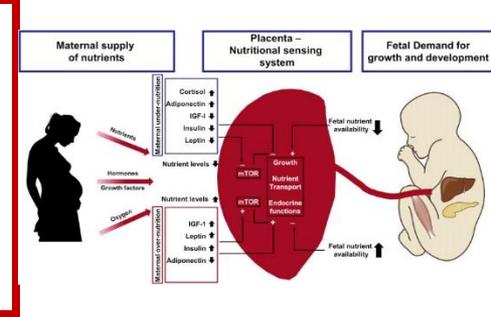
- **Global MUN IUGR fetuses**
- **Surface area (Exchange Villi)**
- **Barrier Thickness**
- **Cell Composition**
 - [sibley 1997, aherne 1966](#)
- Trophoblast Apoptosis ↑↑
- Surface Area 70% ↓
- Barrier Thickness 40 % ↑
- Placental Migration to Advantageous Area



Transport
Capacity



Human placenta Syntitium Nutritional Sensing System



- Adenosine monophosphate – proteinkinase
 - Global energy
- Glucogen Synthase3
 - glucose sensor
- Hexoe Amino signal Pathway
 - glucose, glutamine, acetyl-CoA
- AA response signal transduction Pathway
 - Ess.AA
- mTOR (mechanistic Target of Rapamycin) Complex
 - integrates nutrient and growth factor signaling
- Maternal starvation... impair placentation....IUGR
- Placental-Fetal Unit Adaptive Mechanism and Response
- **Disordered Nutritional sensing system**
 - Jansson 2013, Roos 2009, Rosario 2013



Vasculo – Angio Genesis

- Animal Model Ewes
- Placental Vasculature↑
- VEGF receptor expression↓
- Nutrient transfer↓
 - Redmer 2004
- IUGR Human PI
- NO↓NO synthase ↓
- Vascular resistance↑↑
 - Ziche 2000, xiao 2005 Wu 1998, Itoh 2002, Koumentaki 2002



Nutrient Transfer Capacity Glucose

- Rat Model , Global MUN
- Maternal Glucose ↓..... Fetal Glucose ↓↓
- Glucose Transporter 3 ↓
- Lesage 2002 ↓

- Global MUN Affects placental Transport Mechanism



Nutrient Transfer Capacity Fatty Acids (FA)

- IUGR Placenta
- ↓ Ess.FA → Fetus
- [Magnuss 2009](#)
- ↓ Arachidonic acid
- ↓ Docosa Hexaneic Acid
- ↓ Linoleic acid
- [Araya 1995](#), [Perscy 1991](#), [Cetin 2005](#)
- Altered Microvillous Plasma Membrane Hydrolase Activity



MUN

placental Fetal Transport Critical Factors

1. **NO** ↓ ↓ **NUTRIENT TRANSPORT** wu 2004
2. **Glucocorticoids** ↓ **glucose** transportLangdown 2001
3. **Imprinted placental gene**

MICE- RATS

- ↓ PLACENTA IGF2 EXPRESSION
- ↓ PLACENTAL GROWTH
- Sibley 2003



MUN

Hormone Secretions & Modulations

- Affects
- Maternal- placental- Fetal hormone secretions and appropriate Balance



MUN

Hormone Secretions & Modulations

- Glucocorticoids
 - Excessive exposure to Endogenous **Corticoids**
 - ↓ fetal growth.... **Anxiety Disorder** in Later Life
 - **Disturbed hypothalamo- pituiter-adrenal axis** in **Newborn**
 - ↑ basal corticosteron
 - **Cognitive defects**
 - Wellberg 2000, Levitt 1996



MUN

Hormone Secretions & Modulations

- Insulin Like Growth Factor (IGF)
- Periconceptional & Pregnancy Animal Model (sheep)
- Fetal insulin
- IGF1
- IGFBP3



Fetal Growth

Altered Fetal Programming

- Hills 1996, Osgerby 2002, Harrison 2004, Li 2002



MUN

Hormone Secretions & Modulations

Leptin (Adipocin)(Satiety Factor)

- IUGR ↓Leptin
- Appetite Stimulation Pathway (NPY mRNA expression)
- **Supressed Anorexigenic pathway**
- **Obesity in Adult Life**
- Jaquet 1999, Toprak 2004, Dubillet 2004, Blache 2000, Air 2002



MUN

Transgenerational Inheritance

- ↓↓ Diet Rat
- SGA newborn
- **Diabetes**
- Males fathered
 - **Diabetes among Progeny**
- Lacagnia 2018



Maternal Overnutrition Obesity and Placenta

- BMI ≥ 30 kg/m²
- Dyslipidemia
exaggerated
 - Macroalbuminuria
 - Preeclampsia
- Adult Life
 - **Obesity**
 - **Diabetes**



Increasing
per insulinemia,
• Ramsey 2002, Aye 2014
irth, GDM,
ate, \uparrow CS Rate,



Obesity Placental Weight

- # **37482** obes Pregnant Wallace 2012
- ↑ **BMI** ↑ **PI W** ↑ **BW** ↓ **PI Functions**
- ↑ **LBW** mc Donald 2010
- No Effect on **BW** but ↓ **PI Functions** Dube 2012

Obesity Placental HistoMorphology

- Syncytio Capillar membran **thickness** ↑ Roberts 2011
- ↑ lipid Droplets (Rabbits) Tarrade 2013



Obesity

Placental Vascular Functions

Placental Inflammation

- Disordered Endothelium & Smooth Muscle (Preeclampsia) Wadhvani2009, Smart 2009
- Similar observations in Animal Models Jones 2009, Redmer 2009, Wallace 2002, Wallace 2008, Ma 2010

Obesity

Placental nutrient Transfer

- Altered lipid transfer (Child Obesity) Dube 2012
- ↑ Glucose & Amino Acid Transfer
- ↑ Signaling Pathways (IGF, mTOR) Jansson 2013



Obesity Placental Inflammation

- Well correlated Systemic Inflammation
- ↑ Excessive nutrient transport Jones 2009



MUN& Low Birth Weight intrauterine programming

- **Insulin resistance**
- **Type2 diabetes**
- **Hypertension**
- **Physical, mental impairments**
- **Delayed cognitive functions**
- **↑ Adiposity, Obesity**
- **Maldeveloped skeletal muscle mass**
- **Liver developmental and functional disorders**

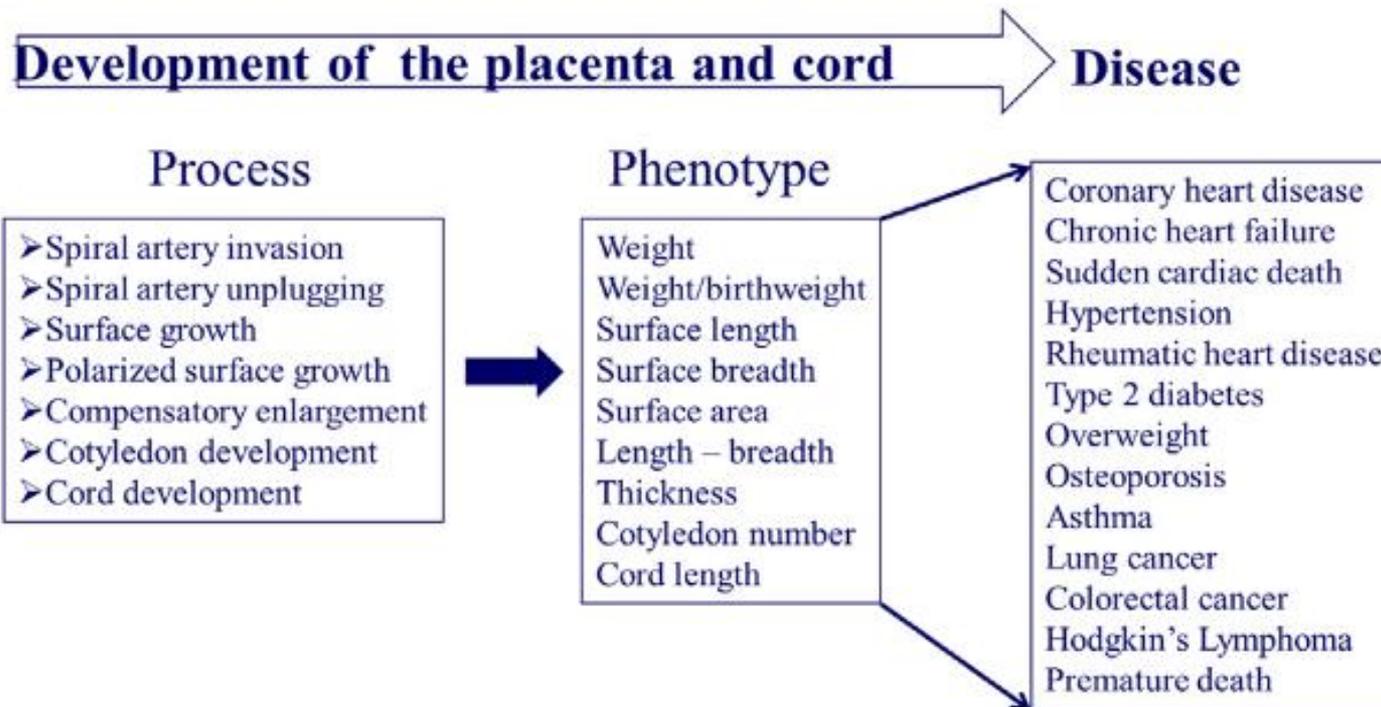


Helsinki Birth Cohort

Barker et al 2005 NEJM

Trajectories of Growth among children who have **coronary events** as **adults**.

20431 case



Pr **Fig. 3.** Variations in the normal processes of development and later chronic disease.



Thank You



Conclusions

- Optimum Maternal Nutrition well before pregnancy
- Balanced diet
- Both UnderNutrition and OverNutrition Hazardous for Placental Functions
- First trimester stress is very important
- Besides immediate Perinatal Outcome
- Long term consequences must take in to account